## REMARKS

### Status of the Claims

Claims 25-29, 43, and 45-47 are pending and claims 43 and 45-47 are under consideration in this application, claims 25-29 having been cancelled for allegedly being drawn to separate inventions.

### Objection to the Specification

With respect to the comments on page 2, line 20, to page 3, line 1, of the Office Action, Applicants respectfully submit that the objection to the specification is moot in light of the above amendment to the specification correcting the relevant citation. In regard to the comments on page 3, lines 1-3, of the Office Action, Applicants respectfully submit that the relevant reference is not cited in support of any conclusions based on "L1 experimentation with astrocytes" but is cited for its finding that "dominant negative Rac expressed in PC12 cells disrupts neurite outgrowth in response to NGF." (see: instant specification, page 4, lines 4-6; and Lamoureux et al., e.g., the Abstract and experiments described on page 638, column 1, second paragraph, and the paragraph spanning columns 1 and 2).

### Priority

Applicants note, and thank the Examiner for, the acknowledgement of the benefit of the October 31, 1997, priority date of the 2,214,841 application.

### 35 U.S.C. § 103(a) Rejection

Claims 1-2, 6-13, 17, and 21-30 stand rejected on the grounds that they are allegedly unpatentable over Kamata et al., U.S. Patent No. 5,851,786 (the '786 patent), Varon et al., U.S. Patent No. 5,134,121 (the '121 patent), Mattson et al., Olson et al. (1994), and Olson et al. (1993). Applicants respectfully traverse the rejection.

From the comments on page 3, line 24, to page 7, line 12, of the Office Action, Applicants understand the Examiner's position to be that in view of the cited art, it would have

been obvious to one of ordinary skill in the art to have performed the methods of the claims under consideration. Applicants respectfully disagree with this position because, as argued below, some of the references lack the disclosure of certain claim elements and/or, at the priority date of the instant application, an ordinarily skilled artisan would not have had the requisite motivation to combine the disclosures of the cited references and hence to carry out the presently claimed methods. Moreover, even if, for the sake of argument, some ordinarily skilled person had been so motivated, she would have had no reasonable expectation of success. In addition, the results of the experiments described in the instant application with respect to treatment of severed optic nerves were, at the priority date of the application, unexpected and surprising.

First, the two cited references (Kamata et al. and the '786 patent) that mention C3 ADP-ribosyl transferase ("C3 ART") not only fail to disclose an essential element of claims 45 and 46 (as acknowledged by the Examiner on page 5, lines 6-10, of the Office Action), they lack the necessary motivation to combine their respective disclosures with one or more putative references disclosing the missing element.

Thus, while the *in vitro* experiments described in Kamata et al. lead the authors to suggest, with substantial reservations (see, e.g., the Abstract line 5 and lines 9-12; and page 427, lines 11-15) to suggest that *C. botulinum* C3 coenzyme ("C3 ART") might have neurotropic activity, the reference does not disclose or even remotely suggest its use in any clinical application, let alone by delivering it to a site of surgery for a traumatic spinal cord lesion. Thus, not only does Kamata et al. not disclose one of the elements of both claims 45 and 46, it also lacks the motivation to combine its disclosure with that of a putative reference disclosing such a treatment modality.

As pointed out in the Amendment and Response filed June 2, 2004, the '786 patent teaches methods for identifying compounds capable of regulating actin polymerization, stress fiber formation and/or focal adhesion assembly as well as methods to treat or control certain diseases with such compounds (see, e.g., Abstract; claim 40; column 1, lines 37-48; column 2, lines 15-19 and 35-36; column 3, lines 30-38; column 17, lines 22-58; column 18, line 8-42). The object of the treatment methods disclosed by the '786 patent is to "regulate cellular

function" (column 2, line 24) and the methods are, in particular, "useful for preventing or treating diseases involving abnormal growth or the migration of cells from one location in an animal to another." (column 17, lines 23-25). It is thus clear that the treatment methods of the '786 patent are directed at inhibiting unwanted cellular activity (e.g., cell growth) in a variety of diseases. On the other hand, the present claims are directed at enhancing a cellular activity (i.e., neuronal axon growth) in order to repair traumatic damage to spinal cord axons. While the '786 patent does refer to treating two nervous system diseases (Parkinson's and Alzheimer's diseases; column 17, line 34), it is clear (from the above cited text) that the inventors contemplated doing so by inhibiting undesirable cellular responses in these diseases rather than by enhancing neuronal axon growth as the present claims require in order to repair traumatic neuronal injury. Thus, not only does the '786 patent not disclose methods or repairing traumatic damage to nerves, it does not contain the slightest suggestion of doing so. Therefore, in addition to not disclosing an element of claims 45 and 46, it lacks the motivation to combine its teaching of using C3 ART with some putative reference disclosing delivery to a site of surgery for a traumatic spinal cord lesion.

With respect to the five references (Varon et al.; the '121 patent; Mattson et al.; Olson et al., 1993; and Olson et al., 1994) cited by the Examiner as providing what is missing from Kamata et al. and the '786 patent, Applicants point out that the factors described by all these references (e.g., nerve growth factor (NGF)) are endogenous mammalian factors that work directly via specific cellular receptors on neurons (See, e.g., the '121 patent, column 1, lines 24-27; and Olson, 1993, page 4, second full paragraph). On the other hand, the factor (C3 ART) disclosed by Kamata et al. and the '786 patent is an exogenous factor derived from bacteria that does not bind to specific receptors and acts by inhibiting the action of a nerve growth inhibitor (Rho) (e.g., Kamata et al., page 42, sentence spanning columns 1 and 2; and the text on page 20, lines 13, of the instant application reciting the findings of Udagawa et al.). Thus, NGF is a factor that occurs naturally in the body of an appropriate mammalian subject and to which neurons in its body are naturally exposed; C3 ART has neither property. In addition, it is clear that from the above that NGF and C3 ART have vastly different mechanisms of action. Thus, even if all five

of these references describing NGF (and related factors) contained the disclosure of the elements of claim 45 and 46 missing from Kamata et al. and/or the '786 patent (as pointed out below, most do not), in light of the above considerations, one of ordinary skill in the art would have been highly skeptical of the success of merely substituting NGF (or related factors) with C3 ART in the methods described by the five references and thus would have been unlikely to do so. In other words, that artisan would have been highly unlikely to combine the disclosures of one or more of the five references with that of Kamata et al or the '276 patent and hence to perform the presently claimed methods. Also in view of the same considerations, if in the unlikely event such an artisan had been so motivated, his or her chances of success would have been minimal.

In addition to the above considerations, the various NGF-describing references have further deficiencies.

Thus, for example, in the section of Varon et al. describing repair of a spinal cord, a nerve tissue "bridge" was used to physically fill the lesion created by excising a segment of the spinal cord and NGF was injected into the spinal cord at a site close to this bridge (paragraph spanning pages 475 and 476 and Figure 2). The treatment was directed at inducing axonal growth into this bridge. The present claims contain no absolute requirement for such a lesion-filling bridge. Indeed, as described in Example II of the present application, treatment of axotomized optic nerves with C3 ART resulted in dramatic increases in growth of the axons across the lesion in comparison with control axotomized optic nerves (e.g., page 28, last paragraph, to page 29, paragraph 2). Thus, as well as lacking the motivation to combine its disclosure with that of the Kamata et al. and/or the '786 patent (for the reasons given above), Varon et al. teaches that an element not specifically required by claims 45 and 46 is essential to the success of the method it describes.

While the '121 patent refers tangentially to the "treatment of injury to the nervous system" (column 7, lines 46-47) and "situations involving nerve damage from traumatic accidents, stroke, and encephalitis" (column 17, lines 51-52) , Applicants are not aware of any disclosure or even a suggestion in it of the delivery of any therapeutic agent (let alone C3 ART) to a site of surgery for a traumatic spinal cord lesion. Thus, in addition to lacking the above-

described "motivation to combine", the '121 patent contains no disclosure or suggestion of the element of claims 45 and 46 missing from Kamata et al and the '786 patent.

Mattson et al. describe the use of various endogenous mammalian growth factors, including NGF, for protecting neurons from excitotoxic or ischemic damage and all the experiments described were carried out *in vitro* (see, e.g., the Abstract). There is no disclosure of enhancing axon growth as occurs in the repair of the spinal cord trauma-caused lesions of the instant claims. Any therapeutic applications mentioned in the reference relate to the brain, and in particular to stroke (see, e.g., the Abstract and page I-139, columns 1 and 2) and there is no mention of spinal cord in this regard. While there is a single mention of surgery in the reference ("The approach of direct delivery through the cranium, although now being used in clinical trials of NGF therapy in Alzheimer's disease,[30] seems impractical for stroke therapy."; page I-139, column 1, first full paragraph), the relevant disclosure is in regard to treatment of brain conditions (i.e., stroke and Alzheimer's disease) and not to spinal cord injury. In summary, Mattson et al. contains no disclosure or even a suggestion of the delivery of any therapeutic agent (let alone C3 ART) to a site of surgery for a traumatic spinal cord lesion. Thus, in addition to lacking the above-described "motivation to combine", Mattson et al. contains no disclosure or a suggestion of the element of claims 45 and 46 missing from Kamata et al and the '786 patent.

While the Olson references do refer broadly to the CNS in their general discussions of neural regeneration (Olson, 1993: e.g., the Introduction and Concluding Remarks; and Olson, 1994: e.g., the Abstract and page S12, column 1, through the paragraph spanning columns 1 and 2 on page S13), in sections describing treatment with factors (including NGF), only treatment of the brain is mentioned (See, for example, Olson, 1993: page 6, column 2, paragraph 1, to end of article; and Olson,1994: page S13, paragraph 2, to end of article). There is in neither reference any disclosure or even a suggestion of the delivery of any therapeutic agent (let alone C3 ART) to a site of surgery for a traumatic spinal cord lesion. Thus, in addition to lacking the above-described "motivation to combine", the two Olson references contain no disclosure or suggestion of the element of claims 45 and 46 missing from Kamata et al. and the '786 patent.

Furthermore, even if the relevant motivation existed, combining the teachings of any two or more of the '121 patent, Mattson et al., or the Olson references would not result in a teaching of the delivery of any therapeutic agent (let alone C3 ART) to a site of surgery for a traumatic spinal cord lesion.

In light of the above considerations, the cited references either lack the disclosure of an essential element of claims 45 and 46 and/or lack the requisite motivation to combine their respective disclosures and hence to perform the methods of the claims under consideration.

Moroever, as an additional indicium of the non-obviousness of the presently claimed invention, the results of the experiments described in Example II of the instant specification showing that C3 ART treatment caused dramatic axonal growth across the lesions of axotomized rat optic nerves (see above) constitute surprising and unexpected results.

In light of the above considerations, Applicants respectfully request that the rejection under 35 U.S.C. §103 (a) be withdrawn.

## CONCLUSION

In summary, for the reasons set forth above, Applicants maintain that the claims under consideration patentably define the invention. Applicants request that the Examiner reconsider the rejections as set forth in the Office Action, and permit the claims under consideration to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number listed below.

Enclosed is a request for an automatic extension of time and a check in payment of the extension in time. Please charge any other fees or make any credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 12552-002001.

Respectfully submitted,

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